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Parental psychological distress and anxiety after a successful IVF/ICSI procedure with and without preimplantation genetic screening: Follow-up of a randomised controlled trial

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ABSTRACT

Background: Infertility treatment has an acknowledged psychological impact on women and their partners; however, information about the development of parental well-being after child birth is inconclusive. Preimplantation genetic screening (PGS) has been suggested to increase the efficacy of infertility treatments, but the effect it may have on parental well-being is unknown.

Aim: To evaluate parental distress and anxiety at one and two years after successful infertility treatment and to explore variables that might affect parental outcome, including PGS and child behaviour.

Study design: Follow-up of a randomised controlled trial (RCT) on the efficacy of PGS.

Subjects: Parents (n = 101) that successfully underwent IVF/ICSI with or without PGS.

Outcome measures: At one and two years, parental distress and anxiety were assessed with the General Health Questionnaire 30 and State Trait Anxiety Inventory, respectively. At two years, child development and behaviour were assessed with the Dutch Bayley Scales of Infant Development-II and the Child Behaviour Checklist 1½–5, respectively.

Results: PGS had no effect on parental distress or anxiety. Child behaviour problems were associated with parental distress and anxiety. There was a main effect of time on parental distress, with distress levels decreasing over time.

Conclusions: We found no objection to PGS related to parental psychological distress and anxiety. When parental psychological problems are present after infertility treatment, the results of this study could be useful to support counselling.

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1. Introduction

Infertility treatment has a known psychological impact on women and their partners [1]. Since assisted reproductive technologies are often a last resort to achieve pregnancy, treatment is stressful for most couples. Following the success of infertility treatment, the future parents often experience happiness as well as stress about the pregnancy [2]. Evidence regarding the development of parental functioning after child birth is inconclusive [3]. Insight into parental psychological functioning, e.g. distress and anxiety, after successful infertility treatment can be useful for determining the need for counselling after treatment.

Furthermore, identifying parameters related to parental distress and anxiety can help to support counselling.

Undergoing in vitro fertilization (IVF) with preimplantation genetic screening (PGS) might be one such parameter. PGS has been suggested to increase the effectiveness of infertility treatment in women of advanced maternal age [4]. These women have an increased risk of numerical chromosomal aberrations in their embryos, resulting in lower pregnancy rates. In PGS embryos are screened for aneuploidy; only embryos with a normal karyotype are selected for transfer to the uterus. There is little available information about the impact of embryo biopsy on parental psychological functioning, and the few studies on this subject mainly focus on parents who are at risk of passing on a genetic disease (preimplantation genetic diagnosis, PGD). One study evaluated PGD and PGS mothers together, and found that anxiety levels increased during treatment but returned to baseline levels at 24 weeks of pregnancy; depression scores did not fluctuate significantly from

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treatment to 24 weeks of pregnancy [5]. Two studies evaluated PGD and PGS couples together, one with follow-up to 4 years and the other to 2 years post-partum; both found no differences in parenting stress and health status compared to patients who underwent standard infertility treatment and normal controls [6,7]. However, it is uncertain whether PGD and PGS should be treated as one group when evaluating psychological health, since PGD and PGS couples have different indications for genetic screening and therefore may differ in medical history and background characteristics.

The aim of this paper is to evaluate psychological distress and anxiety of mothers and their partners at one and two years after successful infertility treatment, and to explore variables, including PGS, that might affect parental outcome. Although PGS nowadays is discouraged due to a lack of evidence for a beneficial effect on the live birth rate, we were interested in the well-being of those parents that already underwent PGS [4,8]. We therefore conducted a follow-up study on parents that were included in a randomised controlled trial (RCT) on the efficacy of PGS. The follow-up study was part of the original research design and consisted of data collection on child and parent functioning up to 2 years after birth. The primary trial outcome (pregnancy rate) was significantly lower after PGS compared to IVF/ICSI only [9]. In the present paper, we focused on the anxiety and distress of the parents. Our hypothesis was that there were no differences in parental distress and anxiety after infertility treatment with or without PGS [6,7]. We had no specific expectations about the effect of the moment of assessing the parents (one versus two years) on the levels of anxiety and distress [3,10]. Maternal anxiety and distress were hypothesised to be higher compared to their partners, as previously reported in the general normal Dutch population [11–13]. Since associations between parental well-being (e.g. depression) and child behaviour problems have been reported in the normal population, we expected to also find this association in our study population [14,15].

2. Methods

2.1. Subjects and procedure

Study subjects in this follow-up were parents of children born after successful IVF/ICSI with or without PGS. Women aged 35 to 41 years, scheduled for infertility treatment between 2003 and 2005 in the University Medical Center of Groningen, the Academic Medical Center in Amsterdam, and two satellite hospitals of these centres, were eligible to participate in a RCT concerning the efficacy of PGS. Participants were given information about the procedure and were invited in advance to participate in the follow-up study. Women were randomly assigned to a treatment group with IVF/ICSI with PGS or a control group with standard IVF/ICSI. Details of the procedure and primary outcomes of the trial have been described elsewhere [9]. The study was approved by the medical ethics committees of the participating hospitals and the Central Committee on Research Involving Human Subjects in the Netherlands.

There were 126 ongoing pregnancies (52 in PGS; 74 in control group). When ongoing pregnancy was achieved (at 12 weeks pregnancy), parents were informed about their allocation. After three pre-partum deaths in each group and the post-partum death of a twin in the PGS group, 119 couples (48 PGS group; 71 control group) with 142 children (57 PGS; 85 control group) remained available for follow-up assessments. All parents provided written informed consent for follow-up.

Parental, gestational, and perinatal characteristics were collected prospectively. At one and two years after child birth, self-assessment questionnaires concerning anxiety and distress were sent to both parents. At two years, a child behaviour questionnaire was also sent to the parents. Parents were asked to return the questionnaires in an enclosed franked self-addressed envelope. At two years, parents were

invited to bring their children to be assessed for mental and motor development by trained psychologists.

2.2. Measurements

The Dutch version of the State-Trait Anxiety Inventory trait questionnaire (STAI) was used to measure trait anxiety [12]. We preferred the trait over the state questionnaire, because trait anxiety can be affected by life events like infertility treatment, but is less distorted by non-controllable circumstantial influences on the person's mood. The trait STAI consists of twenty statements about feelings in general, including ten positive (for example, I feel satisfied) and ten negative statements (for example, I feel nervous and restless), which can each be rated as *almost never* (1), *sometimes* (2), *often* (3), or *nearly always* (4). Missing data were treated according to the manual. The total score had a minimum of 20 and a maximum of 80, with a higher score indicating a higher level of anxiety. The COTAN (the Dutch institute monitoring the quality of psychological test instruments) has deemed the Dutch STAI to be of good reliability and sufficient validity [16].

The General Health Questionnaire 30 (GHQ-30) has been developed to detect non-psychotic psychopathology, particularly emotional and anxiety disorders. It consists of 30 questions about mental health at the moment of answering [13]. Answer options are *better than usual* (0), *as good as usual* (1), *worse than usual* (2), and *much worse than usual* (3). There are different rating methods for the GHQ; GHQ scoring (rating 0,0,1,1) is standard in clinical practice, but we chose to use Likert scoring (0,1,2,3) to make optimal use of the information that each item contained. Missing data were treated according to the manual. The total score had a minimum of 0 and a maximum of 90, with a higher score indicating more distress. The COTAN has deemed the GHQ to be of good reliability and sufficient validity [16].

The Dutch Child Behaviour Checklist 1½–5 (CBCL) was used to assess behaviour problems of the children as perceived by parents [17]. A total problem T-score was calculated. The manual reports a test-retest reliability of 0.85 and a satisfying validity. The mental and psychomotor development of each child was assessed with the Dutch version of the Bayley Scales of Infant Development (BSID II), resulting in a mental development index (MDI) and the psychomotor development index (PDI) [18]. In this study, we analysed the behavioural and developmental child outcomes in association with parental functioning. Detailed information on the children's behavioural and developmental primary outcomes are published elsewhere [19].

2.3. Statistics

Studies have not been consistent with respect to the factorial structure (dimensionality) of the GHQ-30 [20–22]. Therefore, we used confirmatory Mokken scale analysis (MSA), a form of nonparametric item response theory (IRT), to investigate its dimensionality prior to the statistical analysis. IRT is becoming increasingly popular in medical research, both for analysing the dimensional structure of patient-reported outcomes, as well as scrutinizing formal psychiatric diagnoses (for examples, see references [23] and [24]). A discussion of MSA is beyond the scope of this article; we refer the interested reader to Sijtsma and Molenaar [25]. The results of the MSA ($H=0.51$ and $\rho=0.95$) indicated that the GHQ could be considered one-dimensional. Therefore, we chose to use the total score in further analyses.

To investigate possible differences in STAI and GHQ scores between couples that had received PGS treatment versus standard treatment, we used repeated measures multivariate analyses of variance (GLM repeated measures, PASW Statistics 18). The dependent variable in model 1 was the total score on the STAI; in model 2, it was the total score on the GHQ. We included two within-subjects factors: Time (one and two years) and Parent (mother and partner). The most

important between-subject factor was PGS, but we also evaluated the association of a number of other variables that were expected to relate to STAI and GHQ scores. The STAI and GHQ models were built by first separately testing each of the independent variables (between-subject factors and covariates). These independent variables were only included in the final model if we discovered a significant main effect, or two-way interaction effect involving that variable. The following covariates were tested: time to pregnancy (in years), gestational age (GA; in weeks), age of the mother at the beginning of the pregnancy (in years), child behaviour at 2 years (CBCL), and child's mental (MDI) and psychomotor (PDI) development at 2 years. In cases of twins, the CBCL, MDI, and PDI score of one of the twins was randomly selected to be included in the statistical analyses. The tested between-subject factors were: PGS (yes/no), educational level of the mother (lower/intermediate/tertiary), educational level of the partner (lower/intermediate/tertiary), and twins (yes/no). Parental education was classified according to the International Standard Classification of Education (www.uis.unesco.org). An alpha of 0.05 was used.

3. Results

3.1. Descriptive statistics

Fig. 1 displays a flowchart of the follow-up. Two subjects dropped out in the PGS group, due to moving abroad ($n=1$) and assessment burden ($n=1$); five subjects dropped out in the control group, due to moving abroad ($n=1$), being untraceable ($n=2$), and assessment burden ($n=2$). Five children were born after natural conception and three children (including one set of twins) after intrauterine insemination; these parents and children were excluded from analyses (Fig. 1). Finally, 101 children (42 PGS; 59 Control) and their parents

remained available for analyses. Table 1 displays parental, pre- and perinatal, and infant characteristics.

Table 2 shows the results of the follow-up assessments. Two STAI forms from mothers and one STAI form from a partner at 2 years had to be excluded due to missing items. The mean STAI scores of the total group corresponded to the third and fourth deciles of the norm population [12]. The mean GHQ scores were slightly lower compared to the norm population [11]. Both STAI and GHQ scores did not differ between the PGS group and the control group. STAI, GHQ, MDI, PDI, and CBCL scores were all normally distributed. No differences in CBCL, MDI, and PDI scores were found between groups when all twins were included or when only one child of each pair of twins was randomly included for analysis. We therefore assumed that the randomly selected children were representative of the total group of children.

3.2. Model building

For both STAI and GHQ, the within-subject factors Time and Parent were tested first. Next, the independent variables (between-subject factors and co-variables) were tested. Independent variables were only included in the final model if associated with a significant main effect or two-way interaction effect.

3.2.1. STAI (Model 1)

Time and Parent did not have a significant main effect on STAI - implying that STAI scores were stable over time, and that mothers had anxiety levels comparable to their partners. PGS, twins, time to pregnancy, gestational age, age of the mother at the beginning of the pregnancy, and PDI score of the child on the STAI did not have significant main effects. PGS did not have a significant two-way interaction with any of the other variables. The educational level of the

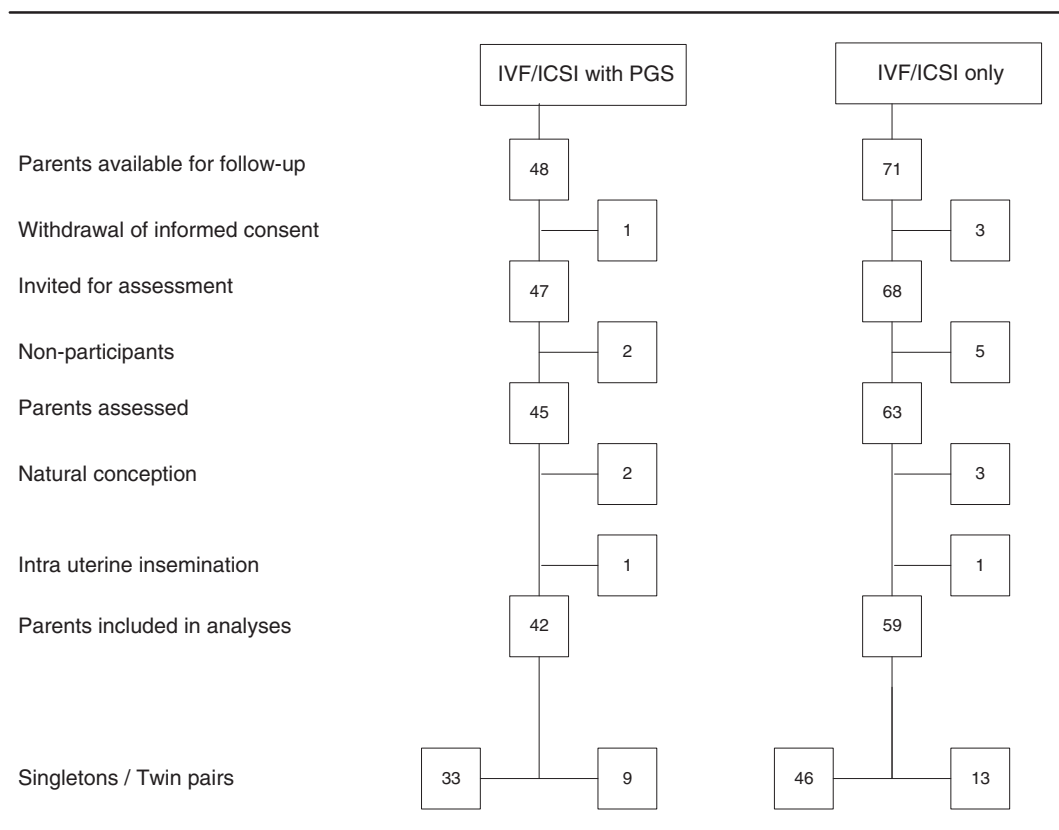


Fig. 1. Eligibility and participation of parents and children.

Table 1
Parental, pre- and perinatal and infant characteristics.

| | Total N = 101 | IVF/ICSI + PGS N = 42 | IVF/ICSI only N = 59 | P-value |
|---|---------------|-----------------------|----------------------|---------|
| <i>Parental characteristics</i> | | | | |
| Treatment | | | | 1.00 |
| IVF | 62/101 (61) | 26/42 (62) | 36/59 (61) | |
| ICSI | 39/101 (39) | 16/42 (38) | 23/59 (39) | |
| Maternal age at conception (years) | 37.2 (1.5) | 36.9 (1.4) | 37.4 (1.6) | .125 |
| Time to pregnancy (years) | 4.1 (2.8) | 3.9 (2.4) | 4.3 (3.0) | .457 |
| Smoking during pregnancy | 5/92 (5) | 3/37 (7) | 2/55 (3) | .388 |
| Alcohol during pregnancy | 2/82 (2) | 1/35 (2) | 1/53 (2) | 1.00 |
| Diabetes mellitus | 2/98 (2) | 0/39 | 2/59 (3) | .516 |
| Pregnancy induced hypertension | 16/98 (16) | 3/39 (7) | 13/59 (22) | .109 |
| Medication during pregnancy | 29/97 (30) | 12/38 (32) | 17/59 (29) | .772 |
| Education mother lower/intermediate/tertiary | 11/37/51 | 4/17/20 | 7/20/31 | .801 |
| Education partner lower/intermediate/tertiary | 13/35/51 | 7/12/23 | 6/23/28 | .408 |
| <i>Birth characteristics</i> | | | | |
| Gestational age (weeks) | 38.6 (2.5) | 39.2 (2.3) | 38.2 (2.6) | .041* |
| Low gestational age (<37 weeks) | 16/101 (16) | 5/42 (12) | 11/59 (19) | .361 |
| Birth weight (grams) | 3254 (696) | 3390 (646) | 3157 (719) | .098 |
| Low birth weight (<2500 g) | 12/101 (12) | 4/42 (10) | 8/59 (14) | .757 |
| Caesarean section | 27/101 (27) | 7/42 (17) | 20/59 (34) | .089 |
| Twin births | 22/101 (22) | 9/42 (21) | 13/59 (22) | 1.00 |
| Male | 55/101 (55) | 24/42 (57) | 31/59 (52) | .699 |
| Apgar 5 min | 10 (6–10) | 10 (6–10) | 10 (6–10) | .684 |
| Hospital admission | 35/101 (35) | 11/42 (26) | 24/59 (41) | .132 |

Data were expressed in n / total n (%); mean (sd); median (range); n where applicable.

Concerning twins, only data of the at random selected child are included.

*Statistically significant.

mother and partner did not have significant main effects, but these variables did have significant interactions with Parent, implying that the difference between partners in reported STAI scores differed among educational levels. Closer inspection of this interaction effect revealed that mothers with a lower level of education reported less anxiety (lower STAI total score) than their partners, whereas mothers with intermediate/tertiary education reported more anxiety than their partners. When mothers had a partner with lower education, they reported more anxiety than their partner, whereas mothers that had a partner with tertiary education reported less anxiety than their partner. For mothers that had a partner with intermediate education, there was no difference between them and their partner with respect to reported STAI scores. CBCL score of the child had a significant main effect on overall STAI score. MDI had no significant main effect; however, MDI showed significant two-way interactions with both Time and Parent. Scrutiny of the two-way interactions showed that the association between MDI and STAI scores was stronger for STAI total scores reported at 2 years than for those reported at

1 year, and that the association was stronger for partners than for mothers.

When incorporating educational level of either parent, CBCL score, and MDI score in the same model, the interaction effects of MDI with Time and of educational level with Parent were no longer significant; however, the main effect of CBCL, and the interaction between Parent and MDI remained significant. This implies that the relatively high levels of anxiety reported by partners of mothers with a lower education, partners who have a lower education themselves, as well as mothers who have either an intermediate/tertiary education or a partner with a tertiary education, can be explained by the characteristics (MDI and CBCL score) of their child. The final model can be found in Table 3.

3.2.2. GHQ (Model 2)

Time did not have a significant main effect, implying that GHQ scores were stable over time. However, there was a main effect of Parent; mothers had higher scores (mean = 24.6) than their partners

Table 2
Results of follow-up examination.

| | Total N = 101 | IVF/ICSI + PGS N = 42 | IVF/ICSI only N = 59 | P-value |
|----------------------|---------------|-----------------------|----------------------|---------|
| STAI Mother 1 year | 34 (11), 92 | 32 (11), 37 | 35 (11), 55 | .252 |
| STAI Partner 1 year | 30 (8), 88 | 29 (8), 37 | 31 (8), 51 | .213 |
| STAI Mother 2 years | 33 (8), 94 | 32 (8), 39 | 33 (8), 55 | .312 |
| STAI Partner 2 years | 30 (10), 92 | 30 (9), 39 | 31 (11), 53 | .769 |
| GHQ Mother 1 year | 27 (14), 91 | 27 (15), 36 | 27 (13), 55 | .857 |
| GHQ Partner 1 year | 21 (7), 87 | 22 (7), 36 | 21 (7), 51 | .706 |
| GHQ Mother 2 years | 25 (11), 97 | 26 (11), 40 | 25 (11), 57 | .715 |
| GHQ Partner 2 years | 23 (11), 92 | 22 (9), 39 | 23 (12), 53 | .859 |
| CBCL Total T-score | 46 (9), 99 | 44 (9), 41 | 47 (9), 58 | .165 |
| BSID II MDI | 102 (13), 100 | 101 (13), 41 | 102 (14), 59 | .738 |
| BSID II PDI | 91 (15), 99 | 91 (16), 40 | 92 (14), 59 | .805 |

Data are reported as mean (sd), number of completed questionnaires.

Concerning twins, only data of the at random selected child are included.

Table 3
Repeated measures MANCOVA: final models of STAI and GHQ.

| Effect | STAI (Model 1) ^a | | GHQ (Model 2) ^a | |
|---------------|-----------------------------|----------|----------------------------|----------|
| | F-value | P-value | F-value | P-value |
| Time | 0.65 ^b | 0.423 | 9.91 ^b | 0.002** |
| Partner | 3.72 ^b | 0.057 | 3.47 ^b | 0.066 |
| CBCL | 19.25 | <0.001** | 13.59 | <0.001** |
| MDI | 0.20 | 0.655 | 0.59 | 0.443 |
| PDI | – | – | <0.01 | 0.960 |
| Time × MDI | – | – | 5.09 ^b | 0.027** |
| Time × PDI | – | – | 4.92 ^b | 0.029** |
| Partner × MDI | 9.01 ^b | 0.004** | – | – |

^adf = 1,78 (for all effects).

^bBased on Wilk's Lambda.

**Statistically significant.

Note: the results in this table are based on our final model; only effects of interest are listed.

(mean = 21.3). There were no significant main effects of PGS, twins, time to pregnancy, gestational age, educational level of the mother and partner, and age of the mother at the beginning of the pregnancy. PGS did not have a significant two-way interaction with any of the other variables. The child's CBCL score had a significant main effect on parent's GHQ scores. MDI and PDI did not have a significant main effect, but both had significant two-way interactions with both Time and Parent on GHQ.

When incorporating CBCL score, MDI, and PDI score in the same model, the main effect of Parent and the interaction effects of MDI/PDI with parent were no longer significant. In this model, Time and CBCL score each had a main effect, and we observed interaction effects of MDI/PDI with Time (see Table 3). Inspection of the partial correlations of the MDI score with GHQ score (corrected for CBCL and PDI score) and of the PDI score with GHQ score (corrected for CBCL and MDI score) for the two different time-points, indicated that the associations diminished over time. It should be noted the correlations were weak to begin with: 0.1 for each correlation at 1 year.

4. Discussion

The aim of this study was to evaluate parental psychological distress and anxiety at one and two years after successful infertility treatment, and to explore the impact of several variables, including PGS, on parental distress and anxiety. We found no effect of PGS on parental distress and anxiety after successful infertility treatment, which confirmed our hypothesis. This result is comparable to those found in studies that included both PGS and PGD parents [6,7], providing further evidence of comparable psychological health between PGS and PGD parents.

To examine whether there was evidence of parental concerns about child development after PGS, we looked at the effects of PGS and child characteristics (CBCL, MDI, PDI) on parental functioning. We found no such significant interaction effects, meaning that even in cases where the child had developmental or behavioural problems, parental well-being was not associated with PGS. No evidence was found to validate concerns about late effects of PGS.

We did find significant effects of child behaviour on parental distress and anxiety. Other studies have reported positive associations between child behaviour problems and parental dysfunction in a normal population [26,27]. In the present study, parental anxiety and distress were the main outcome variables and child functioning was regarded as a covariate. The relation between parent and child functioning has mainly been described as from parent to child, although effects from child to parent have also been considered [28]. Our study design did not allow conclusions about the direction of this relation. We further found several interaction effects with child development, although some interaction effects concerning education and parent (mother or partner) disappeared when adding child characteristics into the models. It seems

that child characteristics are important in parental functioning, and that specific groups of parents are more sensitive when faced with child behaviour problems. Our findings suggest that when there is an indication for counselling after infertility treatment, attention should be paid to parental functioning as well as child behaviour and parent–child interaction problems.

As most studies on the effect of infertility treatment focus on the mothers, it is interesting that the present study found an association between child behaviour and parental functioning of partners as well. The relation of paternal functioning and child behaviour in the normal population has received increased attention over the last few years [14]. Our results suggest that the role of the partner (in most cases the father) should not be underestimated. Further studies are needed to examine the role of paternal functioning after infertility treatment.

We found a main effect of time on parental distress, with parental distress decreasing over time. Trait anxiety remained stable over time. One of the few studies that examines post-partum parental functioning after IVF/ICSI at two different time-points also found stable levels of both trait and state anxiety [10].

Several assumed predictors (e.g. maternal age, time to pregnancy, gestational age, and having twins) were not associated with parental distress and anxiety. Time to pregnancy, for example, has been reported to be associated with increased anxiety [29], but this variable showed no significant effect on parental distress or anxiety in our study. The absence of an effect of the above-mentioned variables might be explained by the specific study population, which included only parents that had a successful pregnancy. For these couples, becoming parents is the achievement of something long wanted. Compared to parents that conceive naturally, it has been suggested that parents going through infertility treatment perceive their children as being more special [30]. The joy of finally having a child might overrule factors that otherwise would have an effect on parental well-being. It has also been suggested that parents who underwent infertility treatment believe that they should feel only positive emotions towards parenthood, and therefore ignore negative feelings [3]. We speculate that these factors might explain the absence of observed effects of the studied predictors.

The randomised controlled multicentre design was one of the strengths of this study. There were no differences in parent and child characteristics between the PGS group and the control group, meaning that possible differences in outcome could be ascribed to the intervention with more certainty. Both medical outcomes and psychological data were collected. The longitudinal data collection in the present study made it possible to determine the development of psychological functioning up to two years after child birth. Most studies that measure post partum distress focus on the mother, whereas our study obtained information from both parents. A weakness of this study design is that no information on mental health was gathered during or before the start of infertility treatment. Such information might have given insight in the development of distress patterns during and after treatment, and the causal impact of treatment. No data were collected from the people that did not finish infertility treatment. This means that we cannot rule out that our results are influenced by including only psychologically healthy people that endure infertility treatment. The parents in our study are a very specific population; including data of parents that conceived naturally, instead of using norm data, would have allowed better comparison of parental functioning. Future studies are needed to evaluate mental health outcomes of parents after infertility treatment in comparison with parents who conceived naturally and those who underwent infertility treatment but did not achieve pregnancy.

In conclusions, our results showed that child behaviour was associated with parental anxiety and distress in our study population, while PGS was not. The importance of assessing mental health outcomes of invasive medical treatments is increasingly acknowledged. When parental psychological problems are present after infertility treatment, the results of this study could be useful to support counselling.

Conflict of interest statement

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